Original Article

Efficacy and Safety of Reslizumab in Patients with Severe Asthma with Inadequate Response to Omalizumab: A Multicenter, Open-Label Pilot Study

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What is already known about this topic? Many patients with allergic eosinophilic asthma can qualify for different biologic therapies. In this clinical context, omalizumab is usually stated to be the first-line option, but there is a lack of information on the effectiveness of anti−IL-5 mAbs if this drug fails to control asthma.

What does this article add to our knowledge? This is the first prospective study to demonstrate the efficacy of using reslizumab in a patient population with severe allergic and eosinophilic asthma whose asthma was unresponsive to a biologic treatment targeting the IgE pathway.

How does this study impact current management guidelines? This study can help clinicians to consider therapeutic alternatives in patients with severe asthma whose health-related quality of life is strongly affected.

BACKGROUND: Patients with severe allergic and eosinophilic asthma could qualify for different biologic therapies.

OBJECTIVE: To evaluate the efficacy and safety of weight-based intravenous reslizumab dosing in patients who have previously failed therapy with omalizumab.

METHODS: We carried out a 24-week prospective, multicenter, open-label, single-group, self-controlled study in patients with severe eosinophilic asthma who had previously failed to respond to omalizumab. The main objective was to determine whether treatment with reslizumab significantly improved asthma

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Abbreviations used
ACQ- Asthma Control Questionnaire
ACT- Asthma Control Test
ATS- American Thoracic Society
ERS- European Respiratory Society
FENO- fraction of exhaled nitric oxide
ICS- inhaled corticosteroid
IQR- interquartile range

symptoms assessed by the Asthma Control Test (ACT) at week 24. Secondary objectives were to evaluate symptoms at weeks 4 and 12, change in FEV_1 at week 24, and the incidence of severe exacerbations over the study period.
RESULTS: Twenty-nine patients (62.1% women, median age, 50.8 years) were included in the study. The median ACT score significantly increased from 13.0 (interquartile range, 8.0-18.0) at baseline to 21.0 (interquartile range, 14.0-24.0) at 24 weeks ($P = .002$). Only 2 of 29 patients developed at least 1 severe exacerbation during follow-up and none of them required hospitalization. Overall, 15 of 25 patients (60%) were considered as being controlled (ACT score of ≥20 and no exacerbations) at week 24. The percentage of patients who were receiving daily systemic corticosteroids significantly decreased from 72.4% to 52.0% ($P = .019$). Adverse events were mostly moderate and within the range of previously reported side effects with reslizumab.
CONCLUSION: Reslizumab is an effective and safe option for patients with severe eosinophilic asthma and a history of omalizumab failure. **(J Allergy Clin Immunol Pract 2019;7:2277-83)**

Key words: *Asthma; Asthma management; Severe asthma; Omalizumab; Reslizumab*

INTRODUCTION

Asthma is a heterogeneous chronic disease of the airways that can be stratified across several phenotypes and endotypes.[1] Most patients with asthma are well controlled by standard inhaled therapies, but approximately 4% of the total adult asthma population needs additional biologic therapies because of uncontrolled asthma and/or recurrent exacerbations, often requiring prolonged courses of oral corticosteroids.[2] Severe asthma has a strong impact on the patient's health-related quality of life and health care resource utilization.[3] It has been reported that nearly half of this population shows an eosinophilic inflammatory pattern.[4] Such patients can benefit from add-on biologic therapies targeting IL-5, given the key role played by this cytokine in inducing, maintaining, and amplifying airway eosinophilia. Different biologic agents targeting IgE (omalizumab), IL-5, and the IL-5 receptor (mepolizumab, reslizumab, and benralizumab) are currently available. It is difficult to choose the optimal treatment for a patient—with allergic and eosinophilic asthma—who could qualify for different biologic therapies. In this clinical scenario, some authors support the use of omalizumab as a first-line option,[5] but there is a lack of information on the effectiveness of other biologic agents if this drug fails to control asthma. To our knowledge, only 1 published study addressed this issue, and this *post hoc* analysis of subgroups of patients from 2 randomized controlled trials concluded that "in the atopic phenotype of patients with severe eosinophilic asthma and a prior history of omalizumab use, mepolizumab was effective in reducing exacerbations and improving outcomes related to asthma control."[6]

Reslizumab is a humanized mAb of IgG_4 subtype against IL-5 that has been proven to significantly reduce exacerbations in patients with asthma inadequately controlled on at least a medium-dose inhaled corticosteroid (ICS) and greater or equal to 400 eosinophils/μL in peripheral blood.[7] The aim of this study was to evaluate the efficacy and safety of reslizumab in patients with severe asthma who are both allergic and eosinophilic and have previously failed therapy with omalizumab.

METHODS

We carried out a 24-week prospective, multicenter, open-label, single-group, self-controlled study in 10 tertiary centers across Spain. The first patient was included in April 2017, and the last patient's last visit was in March 2018. The main objective was to determine whether treatment with intravenous reslizumab significantly improved asthma symptoms assessed by the Asthma Control Test (ACT) at week 24. Secondary objectives were to evaluate symptoms at weeks 4 and 12, change in FEV_1 at week 24, and the incidence of severe exacerbations over the 24-week study period.

The final study protocol was approved by Galicia's Ethics Committee (Cod 2017/117) and the local ethics committees of the participating centers. The study was conducted in accordance with the latest version of the Declaration of Helsinki.

Subjects

Patients were included after written informed consent was obtained according to the study protocol. The inclusion criteria were as follows: (1) patients aged between 18 and 70 years; (2) who met the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines[8] definition of severe refractory asthma; (3) with history of omalizumab failure due to lack of effectiveness (persisting severe exacerbations and/or uncontrolled symptoms in patients with a poor or moderate response in the global evaluation of treatment effectiveness scale[9]) after a minimum of 16 weeks of treatment and/or adverse side effects leading to discontinuation of the drug; and (4) blood eosinophil count of 400/μL or more at least once in the 3-year period before visit 1 or at this initial visit. Patients were excluded if (1) they were diagnosed with asthma-chronic obstructive pulmonary disease overlap; (2) they had a smoking history of 10 or more pack-years; (3) they received the last dose of omalizumab within the preceding 5 months from the date of visit 1; (4) there was previous exposure to another mAb; and (5) any other severe disease was likely to interfere with the conduct of the study.

Definitions

Asthma: It is diagnosed—in accordance with the Spanish Asthma Guidelines[10]—by the presence of symptoms of wheeze, breathlessness, or cough plus a positive bronchodilator test result (significant improvement by >12% and 200 mL in the FEV_1 10 minutes after the inhalation of 200 mg of salbutamol) or a positive methacholine challenge test result (a provocative concentration of methacholine of

<4 mg/mL required to decrease the FEV_1 by 20%) or high fractional exhaled nitric oxide (FENO) levels (>50 ppb).

Severe asthma: According to the international ERS/ATS guidelines, this is defined as asthma that requires treatment with high-dose ICSs plus a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled" or that remains uncontrolled despite this therapy.[8]

Controlled asthma: This is defined as asthma with a composite of ACT score of more than 19, and the absence of exacerbations during the 24-week treatment period.

Severe asthma exacerbation: It is an event characterized by a clinically judged worsening of asthma control as evidenced by worsening symptoms and that resulted in use of systemic corticosteroids and/or hospitalization.[11]

Study protocol

At the initial visit (visit 1), patients were started on reslizumab 3 mg/kg intravenously every 4 weeks and followed up at the respective participating outpatient clinics at 4, 12, and 24 weeks during the study period. At visit 1, researchers obtained and recorded in an electronic clinical research database anthropometric data, smoking history, atopic status assessed by skin prick testing, clinical history and lung function data, presence of comorbidities, pharmacologic treatments, exacerbations, and symptoms assessed by the validated Spanish version of the ACT[12] and by the Asthma Control Questionnaire (ACQ). Lung function, exacerbations during the previous year, ACT score, ACQ score, adverse events, and blood samples to measure absolute and relative eosinophil counts were also collected at every follow-up visit.

Subjects were terminated from participation in the study if they met 1 or more of the following criteria: (1) violation of the study protocol during the study period, (2) lost to follow-up during the study period, (3) consent withdrawal, and (4) intolerable side effects of reslizumab or any severe adverse event related to the study drug.

Spirometry and bronchodilator test

Spirometry was performed at every visit by using equipment and techniques that met standards developed by the Spanish Respiratory Society (SEPAR).[13] We have used the reference values for pulmonary function testing developed by the Barcelona Collaborative Group.[14] Spirometry results included pre-/postbronchodilator FEV_1 (in liters) and % predicted value, forced vital capacity (in liters and percentage of predicted), and the ratio of FEV_1 and forced vital capacity. Bronchodilator response was defined as an increase in postbronchodilator FEV_1 of more than 12% and more than 0.2 L (measured 15 minutes after inhalation of 200 μg of salbutamol, using a spacer) compared with prebronchodilator FEV_1.

FENO was measured by a chemiluminescence analyzer (NIOX Mino, Aerocrine, Stockholm, Sweden) at a flow rate of 50 mL/s, in accordance with the recommendations of the ERS/ATS task force.[15]

Treatment schedule

Bronchodilators, ICSs, antileukotrienes, antihistamines, nasal corticosteroids, and comorbidity-related medication remained unchanged during the study period, whereas the dose of systemic corticosteroids was allowed to be adjusted according to the investigator's judgment. Reslizumab was administered as 3 mg/kg every 4 weeks by intravenous infusion over 20 to 50 minutes in a health care setting by a health care professional prepared to manage anaphylaxis.

Management and treatment of asthma exacerbations were left to the criteria of the investigators, on the basis of current standard of care.[10]

Statistical methods

The sample size was calculated on the basis of the assumption that a 3-point increase in ACT score from baseline to the final visit is a clinically meaningful difference.[16] A sample size of 24 patients would provide a power of 80% with an α error of 0.05. Taking into account a possible loss to follow-up of 25% and considering previous studies,[17] it was decided to enroll 30 patients.

We performed the statistical analysis of the primary and secondary end points in the intention-to-treat population, which included all patients who received at least 1 dose of the study drug, irrespective of possible protocol violations (eg, lost to follow-up or discontinuation of study drug).

Continuous variables were described by medians and interquartile ranges (IQRs), and categorical variables were described by using the relative and absolute frequencies.

To evaluate differences in asthma outcomes between visits, categorical variables were compared using χ^2 analysis. On the basis of their distributions, continuous variables were compared between visits with Wilcoxon matched-pairs signed rank test or Student *t* test. All analyses were performed using SPSS Statistics version 22 (IBM Corporation, Armonk, NY).

RESULTS

Demographic characteristics

Twenty-nine patients were included in the study. Omalizumab had been discontinued in 23 patients (79.3%) because of the lack of effectiveness and in 6 (20.7%) because of side effects (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Demographic and clinical characteristics at visit 1 are presented in Table I. Briefly, 62% were female, the median age was 50 years, 89.6% had positive skin prick test results (this implies that omalizumab was indicated on a compassionate, off-label basis in 3 nonatopic subjects), and 72% were on daily systemic corticosteroids.

Figure 1 shows the flowchart of patients through the study. Three patients were lost to follow-up at any time during the study and 1 was withdrawn from the study because of a serious adverse event (toxicoderma).

Effect on asthma control

For the primary end point at 24 weeks, the median ACT score significantly increased from 13.0 (IQR, 8.0-18.0) to 21.0 (IQR, 14.0-24.0) ($P = .002$). The improvements from baseline were also significant at 4 and 12 weeks: 21.0 (IQR, 13.0-24.0) and 21.0 (IQR, 15.0-24.0), respectively ($P < .001$) (Figure 2, *A*). Sixteen of 25 patients (64%) achieved the minimal clinically meaningful difference (at least 3 points) at the 24-week timepoint.

The median 7-item ACQ score significantly improved from 2.4 (IQR, 1.7-3.6) at baseline to 1.4 (IQR, 0.9-2.7) at 4 weeks ($P < .001$), 1.3 (IQR, 0.6-2.4) at 12 weeks ($P < .001$), and 1.9 (IQR, 0.9-2.6) at 24 weeks ($P = .004$) (Figure 2, *B*). Thirteen of 25 patients (52%) achieved the minimal clinically meaningful difference (at least 0.5 points). The median Asthma Quality of Life Questionnaire score significantly increased from 4.1 (IQR, 3.0-5.1) at baseline to 5.9 (IQR, 4.2-6.3) at 4 weeks ($P < .001$), 6.0 (IQR, 4.5-6.5) at 12 weeks ($P < .001$), and 5.6 (IQR, 4.4-6.6) at

24 weeks ($P < .001$) (Figure 2, *C*). The minimal clinically significant difference of 0.5 points or more in the Asthma Quality of Life Questionnaire was observed in 16 of 25 patients (64%).

Secondary end points: Exacerbations, systemic corticosteroids, and lung function

Only 2 of 29 patients developed at least 1 severe exacerbation requiring initiation of systemic corticosteroids during follow-up and none of them required hospitalization. Overall, 15 of 25 patients (60%) were considered as being controlled (composite of ACT score of ≥20 and no exacerbations) at week 24.

Although the study did not include a corticosteroid-tapering preestablished regimen, the percentage of patients who were receiving daily corticosteroids significantly decreased from 72.4% to 52.0% ($P = .019$). Mean prednisone equivalent dose was 16 ± 14.9 mg at baseline (18 patients) and 19.0 ± 18.2 mg at week 24 (13 patients).

The median FEV_1 increased from 1.6 L (IQR, 1.3-2.3) at baseline to 1.9 L (IQR, 1.3-2.5) at 4 weeks ($P = .1$) and 1.8 L (IQR, 1.2-2.7) at 24 weeks ($P = .1$) (Figure 2, *D*). At the end of the treatment period, 12 patients improved to 0.1 L or more and 8 patients to more than 0.2 L. The median total blood eosinophil count decreased from 330 cells/mm^3 (IQR, 200-500) at baseline to 70 cells/mm^3 (IQR, 20-100) at week 4 and to 70 cells/mm^3 (IQR, 0-100) at week 24. The median FENO value decreased from 43.0 ppb (IQR, 25.6-63.7) at baseline to 34.5 ppb (IQR, 23.3-59.6) at week 24.

Safety

In this study, adverse events were mostly moderate and within the range of previously reported side effects with reslizumab. The only severe adverse reaction to reslizumab during the study was 1 case of toxicoderma (<12 hours after the administration of the fourth dose of the drug, the patient developed symmetrical rash affecting predominantly her trunk and proximal limbs) that completely resolved after stopping reslizumab and treatment with antihistamines and systemic corticosteroids. We believe that this adverse effect was caused by the administration of reslizumab, because there was a clear time relation between the use of the drug and the occurrence of the reaction, and toxicoderma disappeared after medical treatment and it did not relapse after reslizumab withdrawal. Another patient suffered a vertebral fracture that was not deemed to be reslizumab-related. Erythema at the site of administration was observed in 2 patients. The various adverse events are listed in Table E2 in this article's Online Repository at www.jaci-inpractice.org.

DISCUSSION

This proof-of-concept pilot study shows that reslizumab can be an effective alternative therapy for patients with severe eosinophilic asthma who had previously failed to respond to omalizumab. It shows that reslizumab significantly improved symptoms and quality of life as early as week 4 and the improvement was maintained throughout the 24 weeks of the study. The treatment has proven to be safe, and there was only 1 serious reslizumab-related adverse event (toxicoderma) leading to study medication withdrawal. Although the study was neither planned nor powered to detect a reduction in exacerbations, it must be highlighted that only 2 patients developed at least 1 severe exacerbation during the treatment period. Moreover, there was a clinically relevant improvement in FEV_1 (≥0.1 L) in almost half the population. In addition, although the study was not designed to actively taper corticosteroids to the lowest possible dose, a remarkable proportion of patients (20%) were able to discontinue this medication. It is quite possible that this rate might have been improved by applying a predetermined strategy for reducing the dose of systemic steroids, but this remains to be demonstrated. It is also worth mentioning that a high percentage of the study participants (72%) were corticosteroid-dependent. This is not so surprising when considering that this treatment was the only therapeutic alternative for patients with severe uncontrolled asthma before the approval of biologic drugs other than omalizumab, but it should not affect the generalizability of the results to a wider range of patients because, to date, steroid dependence has not been established as a predictor of response to anti−IL-5 drugs.

Very few previous studies have tried to demonstrate that patients with severe asthma who do not respond to omalizumab can be subsequently and effectively treated with anti−IL-5 therapy. A *post hoc* analysis of 2 clinical trials (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma [MENSA] and Steroid Reduction with Mepolizumab Study [SIRIUS]),[18,19] which aimed to evaluate the effect of mepolizumab in patients with severe eosinophilic asthma who had previously been treated with omalizumab, found that the reductions in the rate of exacerbations and in oral corticosteroid dose were comparable regardless of previous omalizumab use. In addition, the 5-item

TABLE I. Characteristics of patients according to the treatment regimen (N = 29)

Variable	Value*
Age (y)	50.8 (42-64)
Sex, female	18 (62.1%)
Positive skin prick test results	26 (89.6%)
IgE (IU/mL)	105 (44.9-212)
Chronic rhinosinusitis	22 (75.8%)
Polyposis	12 (41.4%)
SAHS	2 (6.4%)
ABPA	1.0 (3.4%)
GERD	7 (24.1%)
Obesity†	9 (31%)
Anxiety‡	10 (34.5%)
Depression‡	6 (20.7%)
ACT score	13.0 (8.0-18.0)
ACQ-7 score	2.4 (1.7-3.6)
AQLQ score	4.1 (3.0-5.1)
FEV_1 (L)	1.6 (1.3-2.3)
FEV_1 (% predicted)	54.4 (42-73)
Severe exacerbations in the previous 12 mo	1.0 (0.0-2.0)
≥1 severe exacerbation in the previous 12 mo	17 (58.6)
Annual exacerbation rate	1.8 ± 1.0
Corticosteroid-dependent patients	21 (72.4%)
Eosinophils (cells/mm^3) at baseline	330 (200-500)
FENO (ppb)	43.0 (25.6-63.7)

ABPA, Allergic bronchopulmonary aspergillosis; *ACQ-7*, Asthma Control Questionnaire (7 items); *AQLQ*, Asthma Quality of Life Questionnaire; *GERD*, gastroesophageal reflux; *SAHS*, sleep apnea-hypopnea syndrome.

*Data are median (IQR) or n (%).

†Obesity is defined as body mass index score of ≥30 kg/m^2.

‡Anxiety and depression diagnoses were collected from the medical history. These were assessed by the Hospital Anxiety and Depression Scale.

FIGURE 1. Flowchart diagram of the study.

ACQ and St George's Respiratory Questionnaire scores were reduced with mepolizumab treatment compared with placebo in both omalizumab-experienced and omalizumab-naive patients, pointing toward an improvement in asthma control and quality of life in patients previously treated with omalizumab. In this respect, these results are concordant with ours.

Our study responds to a clinical need, because there are patients with severe asthma, considered as allergic, who have poor response to omalizumab. In the present study, omalizumab had previously been discontinued mostly because of the lack of efficacy in the included patients, although the reason for discontinuation was "adverse events" in 20.7% of the sample. Previous studies report similar figures. In randomized controlled trials, the dropout rate (an index that considers withdrawal due to lack of efficacy and adverse events) ranges from 7.1% to 19.4%. In real-life studies, the dropout rate ranges from 0% to 45.5%.[20] In Spain, the Spanish Severe Asthma Registry found a dropout rate of 18.7%: 10.5% due to lack of efficacy, 5.6% on patients' own initiative, and 2.6% due to side effects.[17] The response to omalizumab does not seem to be related to the baseline eosinophil count, because a recent study shows that a large proportion of patients with severe allergic asthma have a blood eosinophil count of greater than or equal to 300 cells/μL and concludes that omalizumab effectiveness is similar in "high" and "low" eosinophil subgroups.[21]

It has been shown that 100 mg subcutaneous mepolizumab every 4 weeks may not be effective in reducing airway eosinophilia in some patients with severe prednisone-dependent asthma, but higher doses of another anti−IL-5 mAb (intravenous reslizumab) can control the airway eosinophilic inflammation leading to an improvement in asthma control.[22] Our study has a similar design (the patients were sequentially treated with 2 mAbs) but the drugs (omalizumab and reslizumab) belong to a different pharmacological class. Taken together, the 2 studies provide some evidence that asthma control can be gained either by switching between 2 different anti−IL-5 mAbs (when given at different doses) or by switching between biologic drugs that target a related, but different, inflammatory pathway.[23]

This study also emphasizes the effectiveness and safety of intravenous reslizumab in patients with an allergic phenotype, which may have potential clinical implications when deciding the most appropriate biologic therapy for a given patient. In severe allergic and eosinophilic asthma, both IgE and eosinophils are components of a complex inflammatory process in which they have different roles. It is generally accepted that IgE plays a fundamental role in the triggering, development, and chronicity of the inflammatory responses in allergic asthma, whereas eosinophils are final effector cells in this process. The quantitative importance of each mediator is probably different in each individual patient with asthma and the available biomarkers are not precise enough to assess these differences. In our population, most of the patients with asthma (89%) had a positive skin test result and the median eosinophil count at baseline was 330 cells/mm^3. In this clinical scenario, the decision on which drug is the best choice remains difficult and challenging for the clinicians. Because it is generally considered that IgE is the cause of allergic airway inflammation rather than the consequence of this process, omalizumab has been mainly advocated to treat patients with allergy, although some positive outcomes have also been observed in nonallergic ones.[24,25] However, anti−IL-5 are molecules that target the eosinophils, effector cells located at the end stage of the adaptive and innate immunity. Apparently, according to the results of the literature, patients with allergy with a high blood eosinophil count would qualify for both treatments. In this regard, in a *post hoc* analysis of pooled results from 2 randomized controlled trials, benralizumab has been shown to be effective for patients with severe uncontrolled eosinophilic asthma regardless of serum IgE concentrations and atopy status.[26] Nonetheless, no head-to-head studies have been performed to elucidate this issue. Although our study does not pretend to clarify this issue, it shows that at least some of these patients, considered nonresponders to omalizumab, will benefit from anti−IL-5 mAbs.

Our study has some strengths and limitations. To our knowledge, this is the first clinical trial specifically designed to demonstrate that patients who fail to respond to anti−IgE therapy can be rescued with an anti−IL-5 drug. Because of the lack of a control group, a placebo effect cannot be definitely ruled out. Nonetheless, besides the treatment with reslizumab, little else over the course of the study could have caused the observed improvement in the patients' clinical condition. The significant increase in ACT score occurred together with a marked improvement in quality of life, asthma control, and pulmonary function, giving consistency to the overall results. Moreover, the local ethics committee interpreted that the use of a placebo arm could be considered unethical in patients who are mostly being treated with oral corticosteroids and might qualify

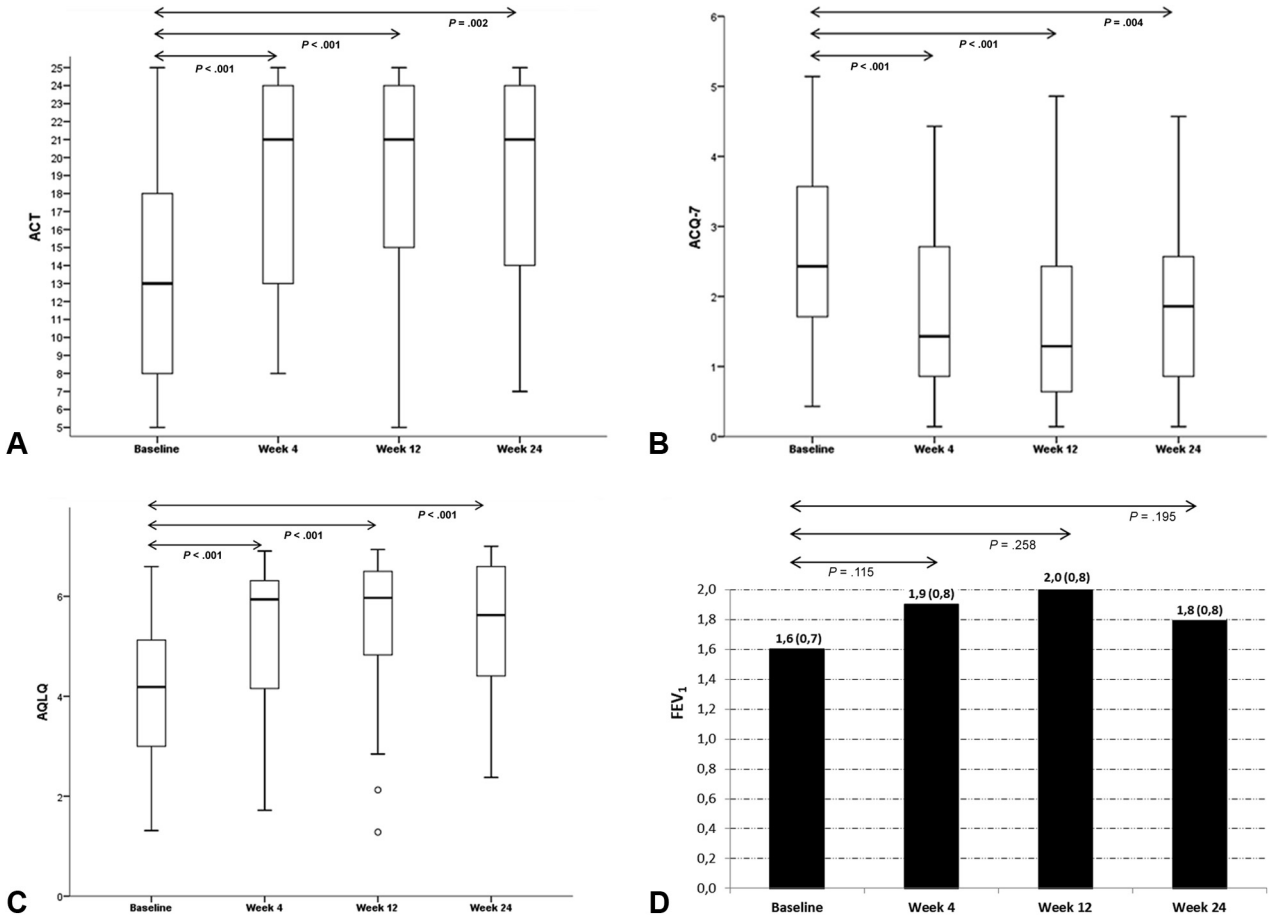

FIGURE 2. Changes in asthma outcomes over the study period. **A,** Changes in ACT score over the 24-week study period. **B,** Changes in 7-item ACQ (ACQ-7) score. **C,** Changes in AQLQ score. **D,** Changes in FEV_1. *AQLQ*, Asthma Quality of Life Questionnaire.

for an existing anti−IL-5 mAb. Another limitation is the relatively small population studied, but the estimated sample size (24 patients) was reached (25 patients completed the study) and it was powered to show statistically significant differences from baseline. In addition, the duration of the trial was too short to explore the effects on exacerbations. However, fewer exacerbations and a positive effect on lung function were observed in most patients.

CONCLUSIONS

This is the first prospective study to demonstrate the efficacy of using an anti−IL-5 drug in a patient population with severe allergic and eosinophilic asthma whose asthma was unresponsive to a biologic treatment targeting the IgE pathway. Reslizumab has been shown to be effective and safe in improving outcomes related to asthma control (symptoms and quality of life) in patients with severe eosinophilic asthma and a history of omalizumab use. The results of our trial should be viewed as hypothesis-generating and in need of testing with a long-term randomized controlled trial to assess the clinical efficacy of targeting the IL-5 pathway in patients with severe eosinophilic asthma with previous omalizumab failure.

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TABLE E1. Reasons for omalizumab discontinuation

		Reason for discontinuation			
		Lack of efficacy			
Patient	Duration of omalizumab treatment (mo)	No. of severe exacerbations	ACT	GETE	Adverse effects
1	6	1	17	Moderate	Generalized arthromialgias
2	3	0	20	Good	Generalized arthromialgias
3	11	4	18	Moderate	
4	23	3	10	Poor	
5	36	1	11	Moderate	
6	23	8	12	Moderate	
7	18	3	9	Poor	
8	12	3	16	Moderate	
9	6	2	17	Poor	Generalized arthromialgias
10	9	6	16	Poor	
11	12	4	12	Poor	
12	3	1	17	Moderate	Generalized arthromialgias
13	4	1	8	Poor	
14	6	0	17	Moderate	Generalized arthromialgias
15	6	0	15	Poor	
16	24	1	9	Poor	
17	32	3	12	Poor	
18	9	2	8	Poor	
19	36	10	12	Poor	
20	8	2	20	Poor	
21	12	6	5	Poor	Generalized arthromialgias
22	24	0	17	Poor	
23	11	3	13	Poor	
24	40	1	12	Poor	
25	9	0	18	Moderate	Generalized arthromialgias
26	11	0	18	Poor	
27	12	2	19	Moderate	Generalized arthromialgias
28	9	3	12	Poor	
29	15	3	16	Poor	

GETE, Global evaluation of treatment effectiveness.
Note. GETE measures response to asthma treatment on a 5-point scale: excellent (complete control of asthma); good (marked improvement in asthma); moderate (discernible, but limited improvement in asthma); poor (no appreciable change in asthma); and worsening of asthma.

TABLE E2. Adverse events

Adverse event	Cases of adverse events	Treatment-related adverse event	Intensity			Treatment discontinued
			Mild	Moderate	Severe	
Toxicoderma	1	1	0	0	1	1
Vertebral fracture	1	0	0	0	1	0
Nasopharyngitis	3	0	3	0	0	0
Tracheitis	1	0	1	0	0	0
Bronchitis	6	0	3	2	1	0
Influenza	4	0	4	0	0	0
Pseudomonas bronchitis	1	0	0	0	1	0
Erythema	2	2	1	1	0	0
Pruritus	2	2	2	0	0	0
Erectile dysfunction	1	0	1	0	0	0
Breast pain	1	0	1	0	0	0
Dizziness	1	0	1	0	0	0
Headache	3	0	2	0	1	0
Vertigo	1	0	1	0	0	0
Diarrhea	1	0	1	0	0	0
Nausea	1	0	1	0	0	0
Gastritis	1	0	1	0	0	0
Abdominal pain	2	0	2	0	0	0
Asthenia	4	4	2	2	0	0
Pyrexia	1	0	0	0	1	0
Arthromialgia	10	3	8	2	0	0
Arterial hypertension	3	0	3	0	0	0